GP1632

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| Application of: | Kohn, et al. |
| Serial No.: | 08/225,478 |
| Filed: | April 8, 1994 |
| For: | Gene Therapy by Administration of Genetically Engineered $CD34^+$ Cells Obtained from Cord Blood |
| Group: | 1632 |
| Examiner: | Stanton |

Assistant Commissioner of Patents
Washington, DC 20231

Sir:

In response to the Final Rejection dated August 20, 1998, reconsideration of the above-identified application is hereby respectfully requested.

The claims stand rejected under 35 U.S.C. 103 as being unpatentable over Anderson, et al., Moritz, et al., and Kohn, et al. in view of either Boyse, et al., or Moore, et al. This rejection is respectfully traversed.

The present invention is directed to a method of expressing a therapeutic agent in a human. As defined broadly in Claim 1, the method comprises administering autologous $CD34^+$ cells obtained from cord blood to the human. The autologous $CD34^+$ cells have been genetically engineered to include at least one nucleic acid sequence encoding a therapeutic agent.

The Examiner's attention is directed to a Declaration Under 37 CFR 1.132 of Donald B. Kohn, filed on March 6, 1997. Accompanying this declaration as Exhibit 2

was a copy of an abstract by Kohn, et al., entitled "Selective Accumulation of ADA Gene Transduced T-Lymphocytes Upon PEG-ADA Dosage Reduction After Gene Therapy with Transduced $CD34^+$ Umbilical Cord Blood Cells." The article was published in Blood, Vol. 86, No. 10, Supp. 1, Abstract 1168 (November 15, 1995).

In the Declaration, Dr. Kohn testified that the work described in the abstract was done by himself, his co-inventors, or others acting on his behalf. The abstract also states that, in May and June of 1993, three neonates that were diagnosed with severe combined immune deficiency, or SCID, were given autologous cord blood $CD34^+$ cells that had been transduced with a retroviral vector including cDNA encoding human ADA. Thus, the claimed invention was reduced to practice in May and June of 1993, which predates the Moritz (published in August 1993), and Moore (published in the summer of 1993) references. Therefore, Moritz and Moore are not effective references against the claimed subject matter of the above-identified application.

Anderson, Kohn, and Boyse, taken in combination, do not disclose or even remotely suggest to one of ordinary skill in the art that one can obtain $CD34^+$ cells from the cord blood of a human, genetically engineer such $CD34^+$ cells to include at least one nucleic acid sequence encoding a therapeutic agent, and administer the genetically engineered $CD34^+$ cells to the human in order to express the therapeutic agent in the human.

Anderson merely discloses the transduction of T-cells with an ADA gene, followed by the administration of the transduced T-cells to human patients in order to treat severe combined immune deficiency. Anderson provides no suggestion to one of

ordinary skill in the art that one may genetically engineer $CD34^+$ cells obtained from cord blood.

Kohn discloses obtaining $CD34^+$ cells from bone marrow, not cord blood. Kohn is directed primarily to the culturing of such cells in the presence of Interleukin -1, Interleukin -3, Interleukin –6, and human mast cell growth factor to provide for improved retroviral transduction of the cells. Thus, Kohn does not render Applicants' claimed method obvious to one of ordinary skill in the art.

Although Boyse discloses the genetic engineering of hematopoietic stem cells from human neonatal or fetal blood to include a heterologous gene, Boyse does not disclose or even remotely suggest to one of ordinary skill in the art that $CD34^+$ cells can be obtained from the cord blood of a human to be genetically engineered with a nucleic acid sequence encoding a therapeutic agent, followed by administration of the genetically engineered $CD34^+$ cells to the human in order to express the therapeutic agent in the human.

Anderson, Kohn, and Boyse clearly do not disclose or even remotely suggest to one of ordinary skill in the art how to obtain $CD34^+$ cells from cord blood of a human. Therefore, Anderson, Kohn, and Boyse do not even remotely suggest to one of ordinary skill in the art that one can express a therapeutic agent in a human by administering to a human autologous $CD34^+$ cells genetically engineered to include a nucleic acid sequence encoding a therapeutic agent.

Applicants and only Applicants have discovered that because the number of circulating hematopoietic progenitor cells drops to levels seen in older children and adults within two days of birth, collection of cord blood cells at birth enables one to obtain

increased quantities of cells such as CD34+ cells, which are useful in gene therapy, in a manner which is safe and efficient. The cited prior art provides no reasonable expectation that autologous CD34+ cells obtained from cord blood and which are genetically engineered with at least one nucleic acid sequence encoding a therapeutic agent, may be administered to a patient to obtain expression of an effective amount of the therapeutic agent *in vivo*. At best, the cited prior art renders it obvious to try to obtain CD34+ cells from cord blood, genetically engineer such CD34+ cells with at least one nucleic acid sequence encoding a therapeutic agent, and administering such genetically engineered CD34+ cells to a patient in order to express a therapeutic agent in the patient. The case law from the Federal Circuit has held that such a standard for obviousness clearly is improper. (See American Hospital Supply Corp. v. Travenol Laboratories, Inc., 223 U.S.P.Q. 577 (C.A.F.C. 1984), at 583; Uniroyal, Inc. v. Rudkin-Wiley Corp., 5 U.S.P.Q.2d 1434 (C.A.F.C. 1988), at 1440.) The Examiner, in formulating his holding of obviousness, also has relied upon the improper use of hindsight gleaned solely from Applicants' disclosure. (See Interconnect Planning Corp. v. Feil, 227 U.S.P.Q. 543 (C.A.F.C. 1985), at 551; In re Dow Chemical, 5 U.S.P.Q.2d 1529 (C.A.F.C. 1988), at 1532; In re Fine, 5 U.S.P.Q.2d 1596 (C.A.F.C. 1988), at 1600.)

Thus, Anderson, Kohn, and Boyse do not render Applicants' claimed method obvious to one of ordinary skill in the art, and it is therefore respectfully requested that the rejection under 35 U.S.C. 103 be reconsidered and withdrawn.

The claims stand rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the treatment of any and all diseases with any and all cells and nucleic acids. This rejection is respectfully traversed.

The Examiner has admitted that the specification is enabling for genetically engineering $CD34^+$ cells obtained from cord blood with the ADA gene, and administering such $CD34^+$ cells to the patient, whereby ADA is expressed in the patient. Because the specification is enabling with respect to the ADA gene, one skilled in the art would expect reasonably that autologous $CD34^+$ cells could be engineered with genes other than the ADA gene, and that such genetically engineered $CD34^+$ cells could be administered to a human in order to express other therapeutic agents in a human. The burden is upon the Examiner to show that one skilled in the art could not genetically engineer autologous $CD34^+$ cells obtained from cord blood with genes other than the ADA gene, and administer such genetically engineered cells to a human in order to express therapeutic agents other than ADA in the human. The "evidence" of nonenablement provided by the Examiner merely states that further work needs to be done with respect to engineering $CD34^+$ cells with genes other than ADA (Kohn, 1995), and that problems remain in various aspects of gene therapy (Orkin). These references, however, do not state that the various problems associated with gene therapy cannot be overcome, or that $CD34^+$ cells cannot be genetically engineered with genes other than the ADA gene. In fact, the Orkin paper states that "More than 100 clinical protocols for gene therapy have been reviewed and approved by the RAC and subsequently approved by the NIH Director. (Table 3). Indeed, 597 individuals have already undergone gene transfer in experiments involving more than a dozen diseases". Thus, even the Orkin report cited by the Examiner provides a reasonable expectation to one of ordinary skill in the art that gene transfer will be successful for expressing a variety of therapeutic agents.

Thus, the Examiner has not met his burden in showing that the specification is not enabling with respect to genes other than the ADA gene. Therefore, for the above reasons and others, the specification provides an enabling disclosure, and it is therefore respectfully requested that the rejection under 35 U.S.C. 112, first paragraph, be reconsidered and withdrawn.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,

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#9705 v1 - Kohn et al Response to Final Rejection

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(Date of Deposit)

..Raymond J. Lillie..
Name of applicant, Assignee, or Registered Representative

..Raymond J. Lillie..
Signature

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Date of Signature